IN THE TITLE:

Please replace the title with the following:

~~**NOVEL G-PROTEIN COUPLED RECEPTORS AND USES THEREFOR**~~

LGR6 NUCLEIC ACIDS AND USES THEREFOR

IN THE SPECIFICATION

At page 3, lines 18-24, please replace the text with the following paragraph:

In one embodiment, an LGR6 nucleic acid molecule of the invention is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more homologous to the nucleotide sequence (*e.g.*, to the entire length of the nucleotide sequence) shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO: 10[[,]] or SEQ ID NO: 12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____, or a complement thereof~~.

At page 5, line 1 through page 7, line 31, please replace the text with the following paragraphs:

In another embodiment, an LGR6 nucleic acid molecule includes a nucleotide sequence encoding a protein having an amino acid sequence sufficiently homologous to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:8[[,]] or SEQ ID NO:11~~, or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~. In a preferred embodiment, an LGR6 nucleic acid molecule includes a nucleotide sequence encoding a protein having an amino acid sequence at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more homologous to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:8[[,]] or SEQ ID NO:11~~, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~.

In another preferred embodiment, an isolated nucleic acid molecule encodes the amino acid sequence of a mouse or human LGR6. In yet another preferred embodiment, the nucleic acid molecule includes a nucleotide sequence encoding a protein having the amino acid sequence of SEQ ID NO: 2, SEQ ID NO:5, SEQ ID NO:8[[,]] or SEQ ID NO:11~~, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~. In yet another preferred embodiment, the nucleic acid molecule is at least 1899, 2175 or 2901 nucleotides in length and encodes a protein having an LGR6 activity (as described herein).

Another embodiment of the invention features nucleic acid molecules, preferably LGR6 nucleic acid molecules, which specifically detect LGR6 nucleic acid molecules relative to nucleic acid molecules

encoding non-LGR6 proteins. For example, in one embodiment, such a nucleic acid molecule is at least 439, 440, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-900, 900-1000, 1000-1500, 1500-2000, 2000-2500, 2500-3000, 3000-3500, 3500-3600 or more nucleotides in length and hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:1, or a complement thereof~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number_____, or a complement thereof~~. In preferred embodiments, the nucleic acid molecules are at least 15 (*e.g.*, contiguous) nucleotides in length and hybridize under stringent conditions to nucleotides 1-1381, 1427-1433, 1690-2341, 2701-2868 and 3379-3637 of SEQ ID NO:1. In other preferred embodiments, the nucleic acid molecules comprise nucleotides 1-1381, 1427-1433, 1690-2341, 2701-2868 and 3379-3637 of SEQ ID NO:1. In another preferred embodiment, the nucleic acid molecules consist of nucleotides 1-1381, 1427-1433, 1690-2341, 2701-2868 and 3379-3637 of SEQ ID NO:1.

In another particularly preferred embodiment, the nucleic acid molecule comprises a fragment of at least 481, 490-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-900, 900-1000, 1000-1500, 1500-2000, 2000-2400 or more nucleotides in length and which hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:4, or a complement thereof~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number_____, or a complement thereof~~. In preferred embodiments, the nucleic acid molecules are at least 15 (*e.g.*, contiguous) nucleotides in length and hybridize under stringent conditions to nucleotides 1-1055, 1231-1290 and 1357-1722 of SEQ ID NO:4. In other preferred embodiments, the nucleic acid molecules comprise nucleotides 1-1055, 1231-1290 and 1357-1722 of SEQ ID NO:4. In another preferred embodiment, the nucleic acid molecules consist of nucleotides 1-1055, 1231-1290 and 1357-1722 of SEQ ID NO:4.

In yet another embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is 167, 170-200, 200-220, 220-240, 240-260, 260-280, 280-300, 300-320, 320-340, 340-360, 360-380, 380-400, 400-420, 420-440, 440-460, 460-480, 490-500, 500-550, 537, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 950-1000, 1100-1200, 1200-1500, or 1500-1899 nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising nucleotides 1-1899 of SEQ ID NO:4 or SEQ ID NO:6~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number_____~~.

In another preferred embodiment, a nucleic acid molecule of the invention is at least 250-500, 500-750, 750-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, 1800-2000, 2000-2174, 2175, 2176-2200, 2200-2400, 2400-2600, 2600 or more nucleotides in length and which hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:7 or 9, or

a complement thereof~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, or a complement thereof~~.

In another preferred embodiment, a nucleic acid molecule of the invention is at least 1-50, 50-100, 100-150, 150-200, 200-250, 250-500, 500-750, 750-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, 1800-2000, 2000-2174, 2175, 2176-2200, 2200-2400, 2400-2600, 2600 or more nucleotides in length and which hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:10 or SEQ ID NO:12, or a complement thereof~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, or a complement thereof~~. In preferred embodiments, the nucleic acid molecules are at least 15 (*e.g.*, contiguous) nucleotides in length and hybridize under stringent conditions to SEQ ID NO:10 or SEQ ID NO:12, or a complement thereof.

In other preferred embodiments, the nucleic acid molecule encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, ~~or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1 or SEQ ID NO:3 under stringent conditions. In yet other preferred embodiments, the nucleic acid molecule encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:5, ~~or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:4 or SEQ ID NO:6 under stringent conditions. In another preferred embodiment, the nucleic acid molecule encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:8, ~~or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:7 or SEQ ID NO:9 under stringent conditions. In another preferred embodiment, the nucleic acid molecule encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:11, ~~or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:11 under stringent conditions.

At page 8, line 29 through page 9, line 3, please replace the text with the following paragraph:

In a preferred embodiment, the protein, preferably an LGR6 protein, includes at least one extracellular domain, at least one leucine-rich repeat, at least one RGD cell attachment site, at least one transmembrane domain, and at least one cytoplasmic domain and has an amino acid sequence at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more homologous to the amino acid sequence of

SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:8[[,]] or SEQ ID NO:11 ~~or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~.

At page 11, lines 5 through 12 please replace the text with the following paragraph:

In another embodiment, the invention features fragments of the proteins having the amino acid sequence of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:8, SEQ ID NO:11 wherein the fragment comprises at least 15 amino acids (*e.g.*, contiguous amino acids) of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:8[[,]] or SEQ ID NO:11 ~~or an amino acid sequence encoded by the DNA insert of the plasmid deposited with the ATCC as Accession Number _____, _____ or _____~~. In another embodiment, the protein, preferably an LGR6 protein, has the amino acid sequence of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:8 or SEQ ID NO:11.

At page 20, lines 6 through 26, please replace the text with the following paragraph:

As used herein, the term "leucine rich repeat" includes a protein domain having an amino acid sequence of about 10-30 amino acid residues and having a bit score for the alignment of the sequence to the LRR domain (HMM) of at least about 5. Preferably, a LRR domain includes at least about 15-28, more preferably about 20-26 amino acid residues, or 22-24 amino acid residues, and has a bit score for the alignment of the sequence to the LRR domain (HMM) of at least about 8, 10, 16, 18, 19, 23, 25 or greater. The LRR domain (HMM) has been assigned the PFAM Accession PF00560 (found at a Pfam website, ~~http://~~genome.wustl.edu/Pfam~~/.html~~). To identify the presence of a LRR domain in a LGR6 protein, and make the determination that a protein of interest has a particular profile, the amino acid sequence of the protein is searched against a database of HMMs (*e.g.*, the Pfam database, release 2.1) using the default parameters (~~http://www.sanger.ac.uk/Software/Pfam/HMM_search~~ see the Pfam website maintained in several locations, *e.g.* by the Sanger Institute (pfam.sanger.ac.uk/Software/Pfam/HMM_search)). For example, the hmmsf program, which is available as part of the HMMER package of search programs, is a family specific default program for PF00560 and a score of 15 is the default threshold score for determining a hit. Alternatively, the threshold score for determining a hit can be lowered (*e.g.*, to 8 bits). A description of the Pfam database can be found in Sonhammer *et al.* (1997) *Proteins* 28(3):405-420 and a detailed description of HMMs can be found, for example, in Gribskov *et al.*(1990) *Meth. Enzymol.* 183:146-159; Gribskov *et al.*(1987) *Proc. Natl. Acad. Sci. USA* 84:4355-4358; Krogh *et al.*(1994) *J. Mol. Biol.* 235:1501-1531; and Stultz *et al.*(1993) *Protein Sci.* 2:305-314, the contents of which are incorporated herein by reference.

At page 22, line 19 through page 24, line 6, please replace the text with the following paragraph:

In another embodiment, the LGR6 proteins of the present invention contain at least one, two, three, four, five, six, or preferably, seven transmembrane domains. As used herein, the term "transmembrane domain" includes an amino acid sequence of about 15 amino acid residues in length which spans the plasma membrane. More preferably, a transmembrane domain includes about at least 20, 25, 30, 35, 40, or 45 amino acid residues and spans the plasma membrane. Transmembrane domains are rich in hydrophobic residues, and typically have an α-helical structure. In a preferred embodiment, at least 50%, 60%, 70%, 80%, 90%, 95% or more of the amino acids of a transmembrane domain are hydrophobic, *e.g.*, leucines, isoleucines, tyrosines, or tryptophans. Transmembrane domains are described in, for example, ~~htto://pfam.wustl.edu/cgi-bin/getdesc?name=~~ see 7tm-1 at the Pfam website at Washington University in St. Louis, pfam.wustl.edu, and Zagotta W.N. et al, (1996) *Annual Rev. Neuronsci.* 19: 235-63, the contents of which are incorporated herein by reference. Amino acid residues 564-590, 598-620, 645-669, 684-704, 731-751, 773-798 and 812-834 of SEQ ID NO:2 comprise transmembrane domains (see Figure 1). Amino acid residues 230-256, 264-286, 311-336, 350-370, 397-417, 440-464 and 478-500 of SEQ ID NO:5 comprise transmembrane domains (see Figure 5). Amino acid residues 333-359, 367-389, 414-439, 453-473, 500-520, 543-567 and 581-603 of SEQ ID NO:8 comprise transmembrane domains (see Figure 8). Amino acid residues 566-590, 599-621, 646-665, 688-709, 728-752 and 777-801 of SEQ ID NO:11 comprise transmembrane domains (see Figure 15).

In another embodiment, an LGR6 includes at least one "7 transmembrane receptor profile" in the protein or corresponding nucleic acid molecule. As used herein, the term "7 transmembrane receptor profile" includes an amino acid sequence having at least about 10-300, preferably about 15-200, more preferably about 20-100 amino acid residues, or at least about 22-100 amino acids in length and having a bit score for the alignment of the sequence to the 7tm_1 family Hidden Markov Model (HMM) of at least 1, preferably 3, more preferably 5-10, preferably 20-30, more preferably 22-40, more preferably 40-50, 50-75, 75-100, 100-200 or greater. The 7tm_1 family HMM has been assigned the PFAM Accession PF00001 (found at a Pfam website, ~~http://~~genome.wustl.edu/Pfam~~/WWWdata/7tm_1.html~~).

To identify the presence of a 7 transmembrane receptor profile in an LGR6, the amino acid sequence of the protein is searched against a database of HMMs (*e.g.*, the Pfam database, release 2.1) using the default parameters (~~http://www.sanger.ac.uk/Software/Pfam/HMM_search~~

see the Pfam website maintained in several locations, *e.g.* by the Sanger Institute (pfam.sanger.ac.uk/Software/Pfam/HMM_search)). For example, the hmmsf program, which is available as part of the HMMER package of search programs, is a family specific default program for PF00001 and score of 15 is the default threshold score for determining a hit. A search was performed against the HMM database resulting in the identification of 7 tm_1 domains in the amino acid sequence of human LGR6 at about residues 404-431 and 553-596 of SEQ ID NO:8 . A search was was also performed against the HMM database resulting in the identification of 7 tm_1 domains in the amino acid sequence of human LGR6 at about and amino acids 635 to 662 and 784 to 827 of SEQ ID NO:11 (see Figure 10). The 7 tm_1 domains in the amino acid sequence of human LGR6 at about amino acids 635 to 662 and 784 to 827 of SEQ ID NO:11 correspond to the 7 tm_1 domains in the amino acid sequence of human LGR6 at about residues 404-431 and 553-596 of SEQ ID NO:8. Alternatively, the seven transmembrane domain can be predicted based on stretches of hydrophobic amino acids forming α-helices (SOUSI server). For example, using a SOUSI server, a 7 TM receptor profile was identified in the amino acid sequence of SEQ ID NO:2, SEQ ID NO:5 (*e.g.*, amino acids 812-834 of SEQ ID NO:2, amino acids 478-500 of SEQ ID NO:5). Accordingly, LGR6 proteins having at least 50-60% homology, preferably about 60-70%, more preferably about 70-80%, or about 80-90% homology with the 7 transmembrane receptor profile of human or mouse LGR6 are within the scope of the invention.

At page 34, lines 22 through 30, please replace the text with the following paragraph:

The nucleotide sequence of the isolated mouse LGR6 cDNA (clone ftmzb048h10) and its predicted amino acid sequence are shown in Figure 1 and in SEQ ID NOs:1 and 2, respectively. ~~A plasmid containing the nucleotide sequence encoding human LGR6 was deposited with American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on _____ and assigned Accession Number _____. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.~~

At page 36, lines 5 through 14, please replace the text with the following paragraph:

The nucleotide sequence of the isolated full length human LGR6 cDNA (clone Fbh150881) and its predicted amino acid sequence are shown in Figure 14 and 15, and in SEQ ID NOs:10 and 11,

respectively. ~~A plasmid containing the nucleotide sequence encoding human LGR6 was deposited with American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on _____ and assigned Accession Number _____. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.~~

At page 37, lines 21 through 29, please replace the text with the following paragraph:

The nucleotide sequence of the isolated human LGR6 cDNA (clone fahr) and its predicted amino acid sequence are shown in Figures 4 and 5, and in SEQ ID NOs:4 and 5, respectively. ~~A plasmid containing the nucleotide sequence encoding human fahr was deposited with American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on _____ and assigned Accession Number _____. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.~~

At page 39, lines 31 to 33, please replace the text with the following paragraphs:

For general information regarding PFAM identifiers, PS prefix and PF prefix domain identification numbers, refer to Sonnhammer *et al.* (1997) *Protein* 28:405-420 and ~~http://www.psc.edu/general/ software/packages/pfam/pfam.html~~ or accessed through the Pfam link at Pittsburgh Supercomputing Center website (psc.edu).

At page 41, line 20 through page 42 line 9, please replace the text with the following paragraphs:

A nucleic acid molecule of the present invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO: 4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____, or _____ a portion thereof~~, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, as a hybridization probe, LGR6 nucleic acid molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning:*

A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

Moreover, a nucleic acid molecule encompassing all or a portion of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____ or _____~~ can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~.

At page 43 line 14 through page 47 line 3, please replace the text with the following:

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, or a portion of any of these nucleotide sequences. A nucleic acid molecule which is complementary to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, thereby forming a stable duplex.

In still another preferred embodiment, an isolated nucleic acid molecule of the present invention comprises a nucleotide sequence which is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more homologous to the entire length of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:12, ~~or the entire length of the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, or a portion of any of these nucleotide sequences.

A. LGR6 Nucleic Acid Fragments

Moreover, the nucleic acid molecule of the invention can comprise only a portion of the nucleic acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____ or _____~~, for example a fragment which can be used as a probe or primer or a fragment encoding a biologically active portion of an LGR6 protein, *e.g.*, a fragment comprising nucleotides 422 to 563 of SEQ ID NO:1, which encodes a leucine-rich repeat of mouse LGR6. Alernatively, a fragment comprising nucleotides 192 to 362 of SEQ ID NO:4, which encodes a leucine-rich repeat of human LGR6 can be used. The nucleotide sequence determined from the cloning of the LGR6 gene allows for the generation of probes and primers designed for use in identifying and/or cloning other LGR6 family members, as well as LGR6 homologues from other species.

The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12 to 15, preferably about 20 to 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, of an anti-sense sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, or of a naturally occurring allelic variant or mutant of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~.

In an exemplary embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is 439, 440, 450-500, 500-550, 537, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 950-1000, 1100-1200, 1200-1500, 1500-2000, 2000-2500, 2500-3000, 3000-3500 and 3500-3600 nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, or 439, 440, 450-500, 500-550, 537, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 950-1000, 1100-1200, 1200-1500, 1500-2000, 2000-2500, 2500-3000, 3000-3500 and 3500-3600 nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~.

In yet another exemplary embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is 481, 490-500, 500-550, 537, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 950-1000, 1100-1200, 1200-1500, 1500-2000, or 2000-2300 nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:4, or

481, 490-500, 500-550, 537, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 950-1000, 1100-1200, 1200-1500, 1500-2000, or 2000-2300 nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:6~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~.

In another embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is 167, 170-200, 200-220, 220-240, 240-260, 260-280, 280-300, 300-320, 320-340, 340-360, 360-380, 380-400, 400-420, 420-440, 440-460, 460-480, 490-500, 500-550, 537, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 950-1000, 1100-1200, 1200-1500, or 1500-1899 nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising nucleotides 1-1899 of SEQ ID NO:4, or SEQ ID NO:6~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~.

In yet another embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is 250-500, 500-750, 750-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, 1800-2000, 2000-2174, 2175, 2176-2200, 2200-2400, 2400-2600, 2600 or more nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising SEQ ID NO:7, or SEQ ID NO:9~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~.

In yet another exemplary embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is 1-50, 50-150, 150-250, 250-350, 350-438, 439, 440, 450-500, 500-550, 537, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 950-1000, 1100-1200, 1200-1500, 1500-2000, 2000-2500, 2500-3000, 3000-3500 and 3500-3600 nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:10, or is 1-50, 50-150, 150-250, 250-350, 350-438, 439, 440, 450-500, 500-550, 537, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 950-1000, 1100-1200, 1200-1500, 1500-2000, 2000-2500, 2500-3000, 3000-3500 and 3500-3600 nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~.

Probes based on the LGR6 nucleotide sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins. In preferred embodiments, the probe further comprises a label group attached thereto, *e.g.*, the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissue which misexpress an LGR6 protein, such as by measuring a level of an LGR6-encoding nucleic acid in a sample of cells from a subject *e.g.*, detecting LGR6 mRNA levels or determining whether a genomic LGR6 gene has been mutated or deleted.

A nucleic acid fragment encoding a "biologically active portion of an LGR6 protein" can be prepared by isolating a portion of the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]]or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, which encodes a polypeptide having an LGR6 biological activity (the biological activities of the LGR6 proteins are described herein), expressing the encoded portion of the LGR6 protein (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of the LGR6 protein.

At page 47, line 23, through page 48 line 13, please replace the text with the following paragraphs:

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, due to degeneracy of the genetic code and thus encode the same LGR6 proteins as those encoded by the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:8 or SEQ ID NO:11.

In addition to the LGR6 nucleotide sequences shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of the LGR6 proteins may exist within a population (*e.g.*, the human population). Such genetic polymorphism in the LGR6 genes may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules which include an open reading frame encoding an LGR6 protein, preferably a mammalian LGR6 protein, and can further include non-coding regulatory sequences, and introns.

At page 49 line 3 through page 52 line 9, please replace the text with the following paragraphs:

Moreover, nucleic acid molecules encoding other LGR6 family members and, thus, which have a nucleotide sequence which differs from the LGR6 sequences of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the~~

~~nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~ are intended to be within the scope of the invention. For example, another LGR6 cDNA can be identified based on the nucleotide sequence of human LGR6. Moreover, nucleic acid molecules encoding LGR6 proteins from different species, and thus which have a nucleotide sequence which differs from the LGR6 sequences of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~ are intended to be within the scope of the invention. For example, a mouse LGR6 cDNA can be identified based on the nucleotide sequence of a human LGR6.

Nucleic acid molecules corresponding to natural allelic variants and homologues of the LGR6 cDNAs of the invention can be isolated based on their homology to the LGR6 nucleic acids disclosed herein using the cDNAs disclosed herein, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 15, 20, 25, 30 or more nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~. In other embodiment, the nucleic acid is at least 30, 50, 100, 150, 200, 250, 300, 307, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2200, 2400, 2600, 2800, 3000, 3200, 3400, 3500 or 3600 nucleotides in length. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% homologous to each other typically remain hybridized to each other. Preferably, the conditions are such that sequences at least about 70%, more preferably at least about 80%, even more preferably at least about 85% or 90% homologous to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50°C, preferably at 55° C, and more preferably at 60°C or 65°C. Preferably, an isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequence of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:7 or SEQ ID NO:10, corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (*e.g.*, encodes a natural protein).

In addition to naturally-occurring allelic variants of the LGR6 sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, thereby leading to changes in the amino acid sequence of the encoded LGR6 proteins, without altering the functional ability of the LGR6 proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of LGR6 (*e.g.*, the sequence of SEQ ID NO:2, SEQ ID NO:5 or SEQ ID NO:8 or SEQ ID NO:11,) without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the LGR6 proteins of the present invention, are predicted to be particularly unamenable to alteration. Furthermore, additional amino acid residues that are conserved between the LGR6 proteins of the present invention and other members of the LGR6 families are not likely to be amenable to alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding LGR6 proteins that contain changes in amino acid residues that are not essential for activity. Such LGR6 proteins differ in amino acid sequence from SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:8, or SEQ ID NO:11, yet retain biological activity. In one embodiment, the isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein comprises an amino acid sequence at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more homologous to SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:8 or SEQ ID NO:11.

An isolated nucleic acid molecule encoding an LGR6 protein homologous to the protein of SEQ ID NO:2, SEQ ID NO:5 or SEQ ID NO:8 or SEQ ID NO:11 can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO:12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced into SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO: 12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~ by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis.

Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in an LGR6 protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an LGR6 coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for LGR6 biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO: 12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

At page 54 line 29 through page 55 line 12 please replace the text with the following paragraph:

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave LGR6 mRNA transcripts to thereby inhibit translation of LGR6 mRNA. A ribozyme having specificity for an LGR6-encoding nucleic acid can be designed based upon the nucleotide sequence of an LGR6 cDNA disclosed herein (*i.e.*, SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10[[,]] or SEQ ID NO: 12~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an LGR6-encoding mRNA. See, *e.g.*, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742. Alternatively, LGR6 mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, *e.g.*, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418.

At page 60 line 19 through page 61, line 13, please replace the text with the following:

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at ~~http://www.gcg.com~~ the gcg page of the website maintained by Accelrys, Inc., San Diego, CA, USA), using either a Blosum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package ~~(available at http://www.gcg.com)~~, using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (*Comput. Appl. Biosci.*, 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to LGR6 nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to LGR6 protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. ~~See http://www.ncbi.nlm.nih.gov~~ (see the website maintained by National Center for Biotechnology Information, Bethesda, MD, USA).

At page 67 lines 3 through 23, please replace the text with the following:

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-LGR6 monoclonal antibody (see, *e.g.*, G. Galfre *et al.* (1977) *Nature* 266:55052; Gefter *et al. Somatic Cell Genet.*, cited *supra*; Lerner, *Yale J. Biol. Med.*, cited *supra*; Kenneth, *Monoclonal Antibodies*, cited *supra*). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (*e.g.*, a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, *e.g.*, the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC® (Manassas, VA) . Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind LGR6, *e.g.*, using a standard ELISA assay.

At page 75 line 24 through page 76 line 17 please replace the text with the following paragraph:

A transgenic animal of the invention can be created by introducing an LGR6-encoding nucleic acid into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The LGR6 cDNA sequence of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:7 or SEQ ID NO:10 can be introduced as a transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of a human LGR6 gene, such as a mouse or rat LGR6 gene, can be used as a transgene. Alternatively, an LGR6 gene homologue, such as another LGR6 family member, can be isolated based on hybridization to the LGR6 cDNA sequences of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10 or SEQ ID NO:12~~, or the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~ (described further in subsection I above) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to an LGR6 transgene to direct expression of an LGR6 protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become

conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of an LGR6 transgene in its genome and/or expression of LGR6 mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding an LGR6 protein can further be bred to other transgenic animals carrying other transgenes.

At page 98 line 20 through page 99 line 2, please replace the text with the following:

An exemplary method for detecting the presence or absence of LGR6 protein or nucleic acid in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting LGR6 protein or nucleic acid (*e.g.*, mRNA, genomic DNA) that encodes LGR6 protein such that the presence of LGR6 protein or nucleic acid is detected in the biological sample. A preferred agent for detecting LGR6 mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to LGR6 mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length LGR6 nucleic acid, such as the nucleic acid of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:12 ~~or the DNA insert of the plasmid deposited with ATCC as Accession Number _____, _____ or _____~~, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to LGR6 mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

At page 113 line 10 through page 114, line 13, please replace the text with the following paragraphs:

The sequence of the entire clone was determined and found to contain a methionine-initiated open reading frame of about 967 amino acids. Signal peptide algorithms predict that mouse LGR6 (ftmzb048h10) contains a signal peptide (about amino acids 1-23 of SEQ ID NO:2). The mature protein is approximately 943 amino acid residues in length (from about amino acid 24 to amino acid 967 of SEQ ID NO:2). The nucleotide sequence encoding the mouse LGR6 (ftmzb048h10) precursor protein is shown in Figure 1 and is set forth as SEQ ID NO:1. The full length protein encoded by this nucleic acid comprises about 967 amino acids and has the amino acid sequence shown in Figure 1 and set forth as SEQ ID NO:2. The coding region (open reading frame) of SEQ ID NO:1 is set forth in SEQ ID NO:3. ~~The clone comprising the entire coding region of human LGR6 was deposited with the American Type Culture Collection (ATCC), Rockville, Maryland, on _____, 1999, and assigned Accession No. _____, presently in Manassas, Virginia.~~

Based on the mouse ftmzb048h10 sequence, primers were designed and used to screen a human brain library (obtained from Clonetech). Positive human clones were identified. Subsequently, 5' RACE PCR was used to obtain a partial nucleotide sequence shown in Figure 4 and set forth as SEQ ID NO:4. The protein encoded by this nucleic acid comprises about 633 amino acids and has the amino acid sequence shown in Figure 5 and set forth as SEQ ID NO:5. The coding region (open reading frame) of SEQ ID NO:4 is set forth in SEQ ID NO:6. Further DNA sequence analysis of the human fahr clone was used to identify additional nucleotide sequences encoding LGR6, as shown in Figure 8 and set forth as SEQ ID NO:7. The protein encoded by this nucleic acid comprises about 736 amino acids and has the amino acid sequence shown in Figure 8 and set forth as SEQ ID NO:8. The coding region (open reading frame) of SEQ ID NO:7 is set forth in SEQ ID NO:9. ~~The clone comprising the entire coding region of human LGR6 was deposited with the American Type Culture Collection (ATCC), Rockville, Maryland, on _____, 1999, and assigned Accession No. _____, presently in Manassas, Virginia.~~

Further DNA sequence analysis of the human fahr clone was used to identify the full length nucleotide sequences encoding human LGR6, as shown in Figure 14 and set forth as SEQ ID NO:10. The protein encoded by this nucleic acid comprises about 967 amino acids and has the amino acid sequence shown in Figure 15 and set forth as SEQ ID NO:11. The coding region (open reading frame) of SEQ ID NO:10 is set forth in SEQ ID NO:12. ~~The clone comprising the entire coding region of human LGR6 was deposited with the American Type Culture Collection (ATCC), Rockville, Maryland, on _____, 1999, and assigned Accession No. _____, presently in Manassas, Virginia.~~